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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,115	08/15/2005	Brian G Condie	18377-0059	6578

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SUTHERLAND ASBILL & BRENNAN LLP
999 PEACHTREE STREET, N.E.
ATLANTA, GA 30309

EXAMINER	
GAMETT, DANIEL C	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,115	CONDIE ET AL.	
	Examiner	Art Unit	
	DANIEL C. GAMETT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-71* is/are pending in the application.

4a) Of the above claim(s) *24-28,32-58 and 60-71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23,29-31 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/06/2005 07/20/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of claims 1-23, Claims 29-31, in part, and Claim 59, in part, drawn to methods of producing a human neural cell comprising culturing a human pluripotent cell with a ceramide compound, the neural cells produced by said methods, and methods of treating a patient having a neural disease comprising administering said cell to a patient in the reply filed on 10/26/2007 is acknowledged. The traversal is on the ground(s) that Groups I-III relate to a single general inventive concept in that each of the groups relate to methods that involve producing a human neural cell by culturing a human pluripotent cell with an amphiphilic lipid compound. This is not found persuasive because the class of "amphiphilic lipid compounds" could include an unlimited number of compounds with diverse structures; they are not obvious variants of one another. The designated organic active ingredient in Group I is an amide compound; in Group II, designated organic active ingredient is an amine or a nitrogen containing alcohol, and in Group III, the designated organic active ingredient is an ester. These different chemical structures place the claimed methods in separate classifications under both the U.S. and IPC classification systems. The use of these different compounds in the claimed methods represents a technical feature not required by any of the other groups. Group I includes the first recited product, and the first recited methods of making and using the product.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 24-28, 32-58, and 60-71 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/26/2007.

3. Claims 1-23, 29-31, and 59 are under consideration insofar as they are drawn to methods of producing a human neural cell comprising culturing a human pluripotent cell with a ceramide compound, the neural cells produced by said methods, and methods of treating a patient having a neural disease comprising administering said cell to a patient.

Claim Objections

4. Claim 59 is objected to because of the following informalities: Claim 59 is dependent from nonelected claim 44. Claim 59 recites nonelected subject matter, specifically "the composition of Claim 44". Claim 59 was included in the elected group because it drawn to a genus that includes the same product as claim 29. Applicant is required to cancel or amend the claims to remove nonelected subject matter and to remove dependency from nonelected claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The courts have interpreted the first paragraph of 35 U.S.C. 112 to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

a. *The breadth of the claims:* Claim 30 is drawn to methods of treating a patient having a neural disease comprising administration of a neural cell. The term "neural disease" encompasses a great variety of diseases in which different cell types at different

anatomical locations are effected. The underlying pathological mechanisms are still under investigation for many neuropathologic conditions; those that are known involve disparate processes such as neoplasia, cell death due to hypoxia, and trauma. In dependent claim 31, the disease is limited to Parkinson's disease.

b. *The nature of the invention:* As treating any neural disease encompasses an entire branch of medicine, it follows that the invention is complex. For diseases involving cell death, treatment would require that the administered cells replace lost or damaged cells or stimulate the replacement such cells from endogenous pools of progenitor cells. Different diseases require different specific types of neurons and /or glial cells. For tumors, the goal would be to kill or otherwise inhibit the growth of cells.

c. *The state of the prior art and the predictability or lack thereof in the art:* The claimed methods encompasses treatment of diseases that the currently lack effective treatments, such as brain tumors and neurodegenerative diseases. Reviews published after priority date of the instant application indicate that this is a highly complex art and that results are unpredictable. Lindvall et al., *Nature Medicine* 10, S42-S50 (2004), for example, point out that, in each disease, a different spectrum of cell types is affected (Lindvall et al., page S42, left column). Regarding Parkinson's disease, "it remains to be shown that the stem cell-derived neurons, after implantation in animal models, fulfill the requirements of successful graft-that is, to reinnervate most of the of the denervated striatum, restore dopamine release in vivo and substantially improve Parkinson's-like symptoms" (Lindvall et al., page S43, left column). For ALS, recent findings support the "strategy of differentiating stem cells along specific cortical neuronal lineages *in vitro*

and transplanting them so as to reconstruct cortical circuitry" (Lindvall et al., page S48, left column). Further, "it is unknown, though, if such cortical neuronal replacement will work in the brains of individuals with ALS" (Lindvall et al., page S48, left column). The state of the art does not provide enabling guidance that is lacking in the instant specification with regard to stem cell therapies for all neural diseases.

d. The amount of direction or guidance present and the presence or absence of working examples: Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The instant specification provides a method of producing nestin-positive neural progenitor cells from pluripotent cells. The progenitor cells were shown to be capable of differentiating into cells that express markers typical of neurons and glia. The capacity of the cells to become specific types of neuron (e.g. dopaminergic, GABAergic, and etc.) was not tested. S18-treated EB8-derived cells were injected into mouse brains, where they did not form teratomas, migrated to the hippocampus, and integrated into the host's brain tissue (Example 4). However, no treatment of disease was observed or even attempted.

e. The quantity of experimentation needed: The properties of the cells produced by the method disclosed in the instant specification suggest that these cells may ultimately prove to be useful for cell therapy of a variety of neuropathological conditions. The gap between the instant disclosure and the development of therapeutic methods for the broad scope of contemplated conditions is filled with undue experimentation.

7. Claims 1-9 and 12-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods comprising culturing a pluripotent cell with a ceramide compound selected from N2-hydroxy-1-(hydroxymethyl)ethyl)-palmitoylamide ("S16"); N-(2-hydroxy-1-(hydroxymethylethyl)-oleoylamide ("S18"); N,N-bis(2-hydroxyethyl)palmitoylamide ("B16"); N,N-bis(2-hydroxyethyl)oleoylamide ("B18"); N-tris(hydroxymethyl)methyl-palmitoylamide ("T16"); N-tris(hydroxymethyl)methyl-oleoylamide ("T18"); N-acetyl sphingosine ("C2-ceramide"); and N-hexanoylsphingosine (C6-ceramide), does not reasonably provide enablement for methods comprising administration of the all compounds of the formula recited in claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and us the invention commensurate in scope with these claims.

8. The courts have interpreted the first paragraph of 35 U.S.C. 112 to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board

of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

f. *The nature of the invention:* The claims are directed methods of producing a neural cell from a human pluripotent cell. While the control of cell differentiation is generally complex, a particular complication of the instant invention is that human embryonic stem cells frequently respond differently than the mouse embryonic stem cells that are used as models (see Smith, Annu Rev Cell Dev Biol. 2001;17:435-462, esp. page 450).

g. *The breadth of the claims:* The claims are drawn to methods comprising administration of any compound of the general formula recited in claim 1. The formula depicts 5 R groups, wherein R=a saturated or mono- or polyunsaturated (cis or trans) alkyl group having greater than 2 carbon atoms, and R1, R2, R3 and R4 may be the same or different and are saturated or mono-or polyunsaturated hydroxylated alkyl groups, aryl groups, or hydrogen. The number of molecules that may conform to this general formula is incalculable.

h. *The state of the prior art and the predictability or lack thereof in the art:* The art recognizes that endogenous ceramide levels increase during RA-induced differentiation of cultured murine pluripotent PCC7-Mzl stem cells and that exogenous C16, C6, or C2

ceramides cause apoptosis in undifferentiated, but not differentiated cells. (Herget et al., J. Biol. Chem., Vol. 275, Issue 39, 30344-30354, September 29, 2000; see Abstract, Fig. 1). Stimulation of apoptosis by exogenous ceramides was observed to be sensitive to the length of the hydrocarbon chain as C16 ceramide was inactive unless it was first dispersed in organic solvents before addition to the culture medium (see legend to Fig.1).

i. *The amount of direction or guidance present and the presence or absence of working examples:* Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The instant specification teaches that incubation of differentiating mouse ES cells with S16, S18, or C2-ceramide enhanced apoptosis ([0107] in the published application). Only S18 was tested with human ES cells (Examples 9 and 10), which are recited in the instant claims. Thus, only 2 compounds that conform to the formula of claim 1 (other than the C2- and C6- ceramides, which were already known) were shown to stimulate apoptosis, and only one was demonstrated using human cells. S16 and S18 differ from one another by the presence of 2 additional carbons and one unsaturated bond in R of S18 (see FIG.1); R1-4 are identical.

j. *The quantity of experimentation needed:* S16, S18, B16, B18, T16, T18 (Fig. 1 and [0057] in the published application), along with natural ceramides and the cell permeable C2-, and C6-ceremide are described in the instant specification and/or known in the art. These could be tested in the manner taught for S18 in the instant specification without undue experimentation. This small group does not adequately represent the

limitless number of molecules that would need to be tested in order to practice the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 29 and 59 are rejected under 35 U.S.C. 102(e) as being anticipated by US 6833269 (Carpenter), filed May 17, 2000. Claims 29 and 59, is a product-by-process claim drawn to a neural cell derived from a pluripotent cell. Carpenter teaches (throughout whole document) derivation of neurons and neural progenitors (neural cells) from pluripotent human embryonic stem cells (see abstract). The courts have established that if a claimed product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was made by a different process. *In re Thorpe.,* 227 USPQ 964, 966 (Fed. Cir. 1985): *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983).

Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD., whose telephone number is (571)272-1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571 272 0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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DCG
Art Unit 1647
23 January 2008

/David S Romeo/
Primary Examiner, Art Unit 1647